REMARKS

Claims 3, 4, 6 and 8-10 are pending in the instant application. Claims 3 and 4 have been rejected. Claims 6 and 8-10 have been objected to. Claims 3 and 4 have been amended to place them in order for allowance or appeal. After entry of this amendment, Claims 3, 4, 6 and 8-10 will remain pending.

Rejection of Claims 3 and 4 under 35 USC §103(a)

The Examiner has rejected Claims 3 and 4 under 35 U.S.C. §103(a), as allegedly being unpatentable over Chimenti et al. (European Journal of Medicinal Chemistry 1992, 27(6), 633-9) in view of Patani et al. (Chem Rev., 1996, Vol. 96, No. 8, p. 3147-3176). Specifically, the Examiner states:

> Chimenti et al. teaches enzyme inhibitor molecules including the species of
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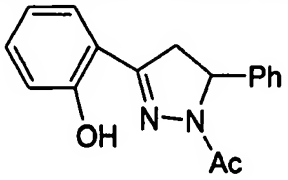
> 
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>
> Chimenti et. al.
> Compound 2a
>
> Patani et al. teaches the methodology of bioisosterism in drug design. Specifically, the reference teaches a method of arriving at the optimal drug by substituting known groups with their bioisosteres in biologically active molecules. In particular on page 3150, table and figure 6 the reference shows in substituting NH_2 for OH on a phenyl ring in a drug molecule.
>
> ...
>
> For example, one of ordinary skill in the art would see the successes such as in table 6 and be motivated to make the same OH to NH_2 substitution and arrive at the claimed invention.

Applicants respectfully traverse the Examiner's rejection. Drug discovery and design is a complex process involving many variables. The pharmaceutical sciences are unpredictable, and it is difficult to predict the activity of a compound without further testing.

The NH_2 and OH substituted purine analogues disclosed in Patani displayed similar binding affinity to the benzodiazepine receptor. The substitution of NH_2 for OH in this

particular class of compounds (substituted 6-(dimethylamino)-9-benzyl-9H-purines) did not greatly affect binding affinity to this particular receptor (benzodiazepine receptor). However, a similar result cannot be expected in every fact pattern for every class of compounds. It cannot be stated that **any** substitution of NH_2 for OH on **any** chemical core structure that binds to **any** receptor would yield compounds of similar potency and activity. In fact, the Patani reference even cautions against such generalizations on page 3151:

> It is important to note that retention of biological activity based on the *in vitro* data can be critical in those instances where differences between bioisosteric analogues exist with regard to *in vivo* parameters which may include absorption, distribution, metabolism, or elimination. While one may only observe retention of activity associated with interaction of drug with the pharmacophore, bioisosteres may differ dramatically in their *in vivo* efficacy.

Applicants do not believe that the Examiner's reasoning applies to the compounds disclosed in the instant application, but should be limited to the fact pattern described in Patani. Furthermore, one skilled in the art would not expect compounds that bind to the benzodiazepine receptor to bind to KSP mitotic kinesins.

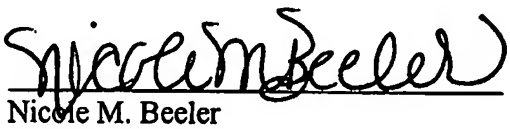
However, without conceding correctness of the Examiner's argument, but to further the prosecution of the instant application, Applicants have amended Claims 3 and 4 to remove $O_a(C=O)_bNR^9R^{10}$ as a substituent for phenyl at the R^2 position. In light of this amendment and the arguments presented, Applicants respectfully request the rejections of Claims 3 and 4 under 35 USC §103(a), be withdrawn.

Objection of Claims 6 and 8-10

The Examiner has objected to Claims 6 and 8-10 as being dependent on a rejected base claim. Applicants believe they have amended Claims 3 and 4 to put them in condition for allowance. In light of these amendments, this objection should be rendered moot. Accordingly, Applicants respectfully request the objection of Claims 6 and 8-10, be withdrawn

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By: 

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